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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,551	05/02/2002	Dan L. Eaton	P3230R1C001-168	9991

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EXAMINER

DUFFY, PATRICIA ANN

ART UNIT PAPER NUMBER

1645

DATE MAILED: 03/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/063,551	Applicant(s) EATON ET AL.	
	Examiner Patricia A. Duffy	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.  
     4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 February 2002 is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
     a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>2002</u> . | 6) <input type="checkbox"/> Other: ____.  |

***DETAILED ACTION***

The preliminary amendment filed 9-9-02 has been entered into the record. Claims 1-6 are pending.

***Priority***

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-6 of this application.

According to the priority statement of 9/9/02, it appears that the claimed subject matter defined in the instant application is not supported by the parent application serial no. 10/006,867. Based on the information given by applicant and an inspection of the patent applications, the examiner has concluded that the subject matter defined in this application is not supported by the disclosure in any of the applications for which Applicants claim priority because the claimed subject matter does not have utility, enablement or written description in any of the prior applications for reasons set forth herein. Accordingly, the subject matter defined in claims 1-6 has an effective filing date of 5-2-02.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 5-2-02 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to 5-2-02.

***Drawings***

The drawings in this application have been approved by the Draftsperson. No further action is required by Applicants.

***Specification***

The disclosure is objected to because of the following informalities:

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The title and abstract of the invention are not descriptive of the now claimed invention. A new title and abstract are required that is clearly indicative of the invention to which the claims are directed.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at least at page 35. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Applicants should review the lengthy specification for other browser-executable code and delete or amend appropriately.

The use of the trademark ATCC<sup>TM</sup> has been noted in this application. They should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. For example, the trademark American Type Culture Collection (ATCC<sup>TM</sup>) needs to be recognized wherever it appears.

***Information Disclosure Statement***

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The information disclosure statement filed 9-10-02 has been considered with the exception of the BLAST sequences. The BLAST results demonstrate that applicants are aware of nucleic acids with identity/homology to the one claimed herein. However, as the BLAST results do not give sufficient identifying information, the Examiner cannot determine if said sequences constitute prior art.

An initialed copy is enclosed.

### *Claim Objections*

Claims 1-6 are objected to because of the following informalities: the claims improperly reference Figures. Referencing figures in a claim is only proper when the information contained therein cannot be represented in any other manner (MPEP 2173.05(s)). Further, the sequence rules require sequences to be claimed by their appropriate sequence identifier number and not Figure number. Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 USC 112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-111, Friday, January 5, 2001.

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Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility due to its not being supported by a specific, substantial and credible utility or, in the alternative a well-established utility.

The claims are drawn to antibodies that bind the polypeptide shown in Figure 46 (SEQ ID NO:46). The polypeptide is encoded by the polynucleotide of SEQ ID NO:45. The specification does not disclose any secondary or tertiary structural features of this polypeptide, nor does it assert that the polypeptide has any homology with known, characterized polypeptides. The instant specification does not disclose any additional information regarding PRO1138 such as biological activity, subcellular location, timing of regulation during cellular differentiation, which hormones or transcription factors regulate PRO1138, and what physiological significance PRO1138 plays. Therefore, it is a totally new, uncharacterized polypeptide with no well-established utility based on the above features of known characterized polypeptide families.

The specification generally asserts that all of the disclosed PRO polypeptides will be useful for a number of purposes; however, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific and substantial. The asserted utilities will each be addressed in turn.

*1) the PRO polypeptide or its antibodies can be used to isolate other polypeptides to which it binds:* This asserted utility is not specific or substantial. Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1138 polypeptides or antibodies thereto. Furthermore, since the specification does not disclose how PRO1138 or its binding partners can be used, significant further research would be required of the skilled artisan to determine how to use the claimed polypeptide or its binding partner. Since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is not substantial.

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*2) the PRO polypeptide or its antibodies can be used as a molecular weight marker:*

This asserted utility is not specific. Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1138 polypeptides or antibodies thereto.

*3) the PRO polypeptide or its antibodies can be used in tissue typing:* This asserted utility is not specific or substantial. With the exception of a few housekeeping genes, all polypeptides have a tissue specific pattern of expression, and thus virtually any polypeptide can be used in tissue typing. Thus, the asserted utility is not specific to PRO1138 of its antibodies.

*4) the PRO polypeptide or its antibodies can be used in therapy in general:* This asserted utility is not specific or substantial. Since a defect in any polypeptide is likely to cause a disease of some sort, every polypeptide is a target for drug development. Thus, the asserted utility is not specific to the claimed PRO1138 polypeptide or antibody. Furthermore, the specification does not disclose a nexus between any specific disease states and a change in amount or form of PRO1138. Significant further research would have to be conducted to identify such a nexus. Therefore, the asserted utility is not substantial.

*5) the PRO polypeptide or its antibodies can be used to identify agonists or antagonists:* Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1138 polypeptides or antibodies. Furthermore, since no activity has been assigned to PRO1138, the assays cannot be conducted until the specific biological activities of PRO1138 are determined empirically. Therefore, the asserted utility is also not substantial.

*6) the PRO polypeptide or its antibodies can be used in tumor/cancer diagnostics or therapeutics:* The teaching of the specification indicate that the polypeptide and antibodies thereto can be used in tumor/cancer diagnostics or therapeutics because the mRNA expression as assessed by quantitative PCR of cDNA libraries is "more highly expressed". In particular, the specification discloses that PRO1138 was tested using

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quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the nucleic acid encoding the PRO polypeptide (specification page 140). The specification alleges that the differential expression in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possession such a tumor. The specification lack utility for the protein and antibodies that bind it because (a) the higher levels of mRNA alleged in the specification have not been demonstrated to be statistically significant and (b) the art recognizes that neither gene copy number or mRNA levels predictably correlate with levels of protein expression. As to point (a) mRNA encoding the PRO1138 polypeptide (DNA 58850-1492) was reported as "more highly expressed in" esophageal and kidney tumors as compared to normal esophageal and kidney tissue (see specification page 141). The specification is devoid of teaching of the number of samples tested, the statistical significance if any of the "more highly expressed" and the specific probe used for the alleged quantitative analysis performed. The data presented are not quantitative and as such, the relevance as compared to the recited control is ambiguous. Further, it appears that normal cells such as stomach and skin express the nucleic acid more highly as compared to tumors. As such, since the cDNA, proteins or antibodies are not described as being specifically correlated with a specific type of cancer the skilled artisan could not distinguish tumors from non-tumors based on the alleged "more highly expressed" criteria only. Therefore, the asserted use as diagnostic marker or targets of therapeutic intervention are not persuasive to impart a specific utility. This relevance of the asserted higher expression very vague, and does not disclose what mathematical calculations, if any, were used to establish significance of the finding across a variety of samples from different patients.



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Therefore, the apparent single data point presented in the quantitative PCR is preliminary at best, and cannot be evaluated or repeated independently by the skilled artisan. Clearly, further research would be required of the skilled artisan to establish the statistical significance if any, and whether and how a probe used in the PCR assay could be used as diagnostic markers or therapeutic targets. Such further experimentation indicates that the asserted utility is not in currently available form for the disclosed nucleic acid of SEQ ID NO:45 encoding the polypeptide of SEQ ID NO:46. Furthermore, the literature indicates that such results are to be evaluated very critically. For example, Hu et al. (2003, *Journal of Proteome Research* 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Therefore, in the absence of a statistical significance of the data and quantitative evaluation it would appear that the relationship between the reported "higher expression" as it relates to tumor formation and role in tumor formation or role in normal cells remains to be established. Consequently, any relevance with respect to using the nucleic acid, protein or antibody for therapeutic purposes remains to be established. As to point (b), it is noted that the art establishes that increased gene copy number does not necessarily lead to increased mRNA expression and increased mRNA production does not necessarily lead to increased protein production and hence the antibody cannot be predictably used for detection of increased polypeptide levels. Pennica et al (*Proc. Natl. Acad. Sci*, 95:14717-14722, 1998) demonstrates an example that gene amplification does not correlate with the protein levels. Haynes et al. (*Electrophoresis*, 19:1862-1871, 1998) found "a general trend" but no significant

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correlation between nucleic acid level and translation and protein levels. Further, Haynes et al teach that polypeptide levels cannot be accurately predicted from mRNA levels and that variances as much as 40-fold or even 50-fold were not uncommon (p 1863). Haynes et al used yeast as an art-accepted model for eukaryotic systems. Additionally, Konopka et al (PNAS 83:4049-52, 1986) states that "Protein expression is not related to amplification of the *abl* gene but to variation in the level of *bcr-abl* mRNA production from a single Ph1 template" (see abstract). Further, the lack of demonstrable correlation of mRNA expression levels with protein levels was so well known in the art at the time of filing, it was reported in a general text book. Lewin (*Genes VI* (1997) Chapter 29, pages 847-848) teaches that the concept that transcription levels do not correlate with protein levels was so well known to the art that it was presented in a textbook. Lewin, *Genes VI* (1997) Chapter 29, pages 847-848 which specifically teaches "... production of RNA cannot be inevitably be equated with production of protein...." (page 487, column 2, last paragraph). This concept reconfirmed by a variety of studies such as that evidenced by Gokman-Polar et al (*Cancer Research* 61:1375-1381, 2001) that indicates the absence of any necessary correlation between increased mRNA levels and increased protein levels. Gokman-Polar et al that teach "Quantitative reverse transcription-PCR analysis revealed that the PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isoenzyme expression is likely regulated at the posttranscriptional/translational level" (see abstract). Gokman-Polar et al show in Figure 6-7 that there is no increasing mRNA expression for any of the isoenzymes, while the protein is significantly overexpressed as shown by Figure 4-5. Given the totality of the evidence provided by Pennica et al, Haynes et al, Konopka et al and Lewin et al, it is clear that those skilled in the art would not assume that an alleged increase in gene copy number or increase in mRNA levels would correlate with increased polypeptide levels. One skilled in the art would have to do further research to determine whether or not the polypeptide levels were higher, and

whether the higher levels were statistically significant. As such, the claimed antibodies that bind the polypeptides do not have utility.

Thus, the proposed use of the antibodies that bind PRO1138 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polynucleotides, encoded polypeptides and antibodies that bind the polypeptides. "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form- there is insufficient justification for permitting an application to engross what may prove to be a broad filed", and "a patent is not a hunting license". "[i]t is not a reward for the search, but compensation for its successful conclusion." Similarly, the other listed and asserted utilities in the specification as exemplified by the other Examples are not particularly disclosed with respect to the claimed antibodies that bind polypeptides or are neither substantial nor specific due to being generic in nature and applicable to a myriad of such anti-polypeptide antibodies. (*Brenner v. Manson*, 148 USPQ 689 (Sus. Ct. 1996). Additionally, the courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use (*In re Kirk and Petrow* (CCPA) 153 USPQ 48). Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the nucleic acid per se, the polynucleic acid encoding the PRO polypeptide or the anti-PRO antibody that binds the polypeptide such that another non-asserted utility would be well established for the instantly claimed compounds.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites an antibody that binds a polypeptide, whereas claim 6 recites an antibody that *specifically* binds the same polypeptide. Neither the art nor the specification provide a clear definition for, or distinction between, "binds" and "specifically binds". Therefore, the metes and bounds of the claimed invention cannot be determined.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6 are rejected under 35 U.S.C. 102(e) as being clearly anticipated Starling et al (WO 01/46260, with priority to US provisional application 60/172,025 filed 23 December 1999) or Starling et al (U.S. Patent Application Publication US 2002/0123617, published Sept 5, 2002 with priority to US provisional application 60/170,025 filed 23 December 1999).

It is noted that the teachings of the WO document and the US Patent Application Publication are identical. As such, only the particulars of the WO document teachings are set forth in detail.

Starling et al teach a human protein APEX-1 represented by SEQ ID NO:4 that is 100% identical as compared with SEQ ID NO:46. Starling et al therefore anticipate claims 1-7, 9 and 11 on this basis. Figure 10 of Starling et al teaches the extracellular domain of APEX-1 (i.e. the instant SEQ ID NO:46 extracellular domain) in an IgFc fusion protein. Starling et al teach the signal sequence of APEX-1 is represented by Met 1-Ala22. Starling et al teach that the APEX-1 protein is composed of a signal sequence, an

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extracellular domain, a transmembrane domain and a cytoplasmic domain (Figure 2). Starling et al teach that the APEX-1 proteins may be fusion proteins comprising heterologous peptides such as a FLAG epitope (see page 10, lines 15-20). APEX protein fragments having APEX activity are taught (see page 15, lines 15-20). Starling et al teach that the domains are particularly useful for generating domain specific antibodies (see page 20, lines 9-19). Starling et al teach antibodies, polyclonal, monoclonal, chimeric, humanized, and human monoclonal antibodies, that bind APEX (see page 20, lines 30-31). Starling et al teach that fragments of antibodies are particularly contemplated are fragments of monoclonal or polyclonal antibodies that bind APEX. Antibodies are elaborated at pages 21-25. Labeled antibodies are contemplated at page 26, lines 1-29. ). As such, Starling et al anticipates the instantly claimed invention.

Claims 1-6 are rejected under 35 U.S.C. 102(e) as being clearly anticipated Khodadoust (U.S. Patent Application Publication, 2002/0004193 published 10 January 2002 with priority to provisional application 60/090,579 filed June 25, 1998).

Khodadoust et al teach antibodies that bind a polypeptide MP-7 represented by SEQ ID NO:2 which is 100% identical as compared to the instantly claimed SEQ ID NO:46. Specifically, Khodadoust et al teach polyclonal, monoclonal, chimeric, humanized antibodies and fragments thereof. The antibodies are optionally labeled for detection of the protein (see [0124]-[0129]). As such, Khodadoust et al anticipate claims 1-6.

#### *Status of the Claims*

Claims 1-6 stand rejected.

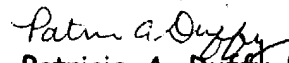
#### *Conclusion*

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

  
Patricia A. Duffy, Ph.D.

Primary Examiner

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